Guest Editorial

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Status Report on Saccharin in Humans

BACKGROUND

On the basis of experimental evidence that the artificial sweetener saccharin causes bladder cancer in rodents (*1-6*), on April 15, 1977, the FDA proposed a ban on saccharin. Under existing law, any substance known to cause cancer in animals or man cannot be allowed on the market as a food additive, so the FDA had no choice in its proposed ban. Saccharin is the only nonsugar sweetener on the market, and the public perceives that it benefits from having it available. Because of this perception, the proposed saccharin ban caused a public outcry that was reflected in mail, telegrams, and telephone calls to members of Congress. Congressional hearings on this subject were held in March and June 1977. In December 1977, Congress imposed an 18-month moratorium on the proposed ban so that more information could be collected.

During the hearings questions arose such as: the rationale for equating carcinogenicity in mice, rats, and other lower animals with carcinogenicity in humans; the justification for administering large unphysiologic doses of a material that presumably do not equate to the lower dose used naturally by humans; and the validity of extrapolating the results of large doses in animals to the situation in humans. The answers to these questions relate to the life-spans of the animals, metabolic rates of lower animals compared to those of humans, and the intent of bioassay tests to demonstrate carcinogenicity if it exists rather than one's missing it or attempting to quantify the level of risk.

Answers to these questions are based on the knowledge that all known carcinogens in man (occurring from natural experiments such as occupational exposures) also cause cancer in some lower animal systems. Two possible exceptions are arsenic and benzene. It is not known whether the reverse is true, namely, that substances carcinogenic for lower animals are necessarily carcinogenic for humans. This proposition would be impossible to prove one way or the other at this time. Precise determinations of thresholds for carcinogens are not attainable at the present time, although the evidence is mounting that, as the dose of many carcinogens is increased, additional factors in terms of cancer causation come into play that may be avoidable at lower doses. Also, for some carcinogens evidence suggests that the carcinogenic response is secondary to a primary response that can be prevented by minimizing exposures.

About the same time that the FDA proposed to ban saccharin, a Canadian study of humans suggested that men with bladder cancer were more frequent users of saccharin than were men without bladder cancer; this implies a possible causal association between use of saccharin and bladder cancer (*7*). At least two U.S. studies showed no apparent association between bladder cancer and saccharin use (*8, 9*).

Because of the conflicting results of the human studies, the FDA and the NCI reviewed the existing human epidemiologic studies of saccharin use and bladder cancer. Although NCI has worked with the FDA for years in the area of drug development, this cooperation represented the first time, to our knowledge, that the NCI joined with a regulatory agency to work out a problem that had attracted enormous public and congressional concern.

REVIEW OF EXISTING STUDIES IN HUMANS

Three types of epidemiologic studies were available for in-depth review: two time-trend studies, three studies of diabetics, and three case-control studies. As with almost every epidemiologic study, these all have limitations, many of which are unavoidable.

The following are the limitations of the two time-trend studies (*10, 11*): 1) If a long latent period existed, the effect would not have been manifest; 2) the average doses may have been too small to cause a measurable effect; 3) high doses may have been accumulated in too few individuals to yield effects detected in a correlation of population trends; and 4) the protocol may not have been able to accommodate associated high-risk factors such as cigarette smoking, occupational exposures, and others.

Limitations of the three studies of diabetics (*12-14*)

ABBREVIATIONS USED: FDA=Food and Drug Administration; NCI=National Cancer Institute; SEER=Surveillance, Epidemiology, and End Results Reporting.

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Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.

include: 1) failure to ascertain which diabetics were saccharin users and which were not, 2) lack of data for individual exposures to other risk factors, 3) presumption that diabetics as a group were at high exposure without direct measurement of exposure to saccharin, and 4) no determination of level or duration of exposure to saccharin.

These five studies provide some assurance that no epidemic of saccharin-induced bladder cancer has occurred. However, the information they provide cannot establish whether artificial sweeteners have a role in the causation of bladder cancer in humans.

Of the three case-control studies reviewed in detail (*7–9*), two were negative and one was positive. They are not criticized for their basic method, but rather for specific design features (many unavoidable). These features include: 1) Controls selected from a hospital were more likely to be overweight or to have other medical problems than were people chosen at random from the population, and thus perhaps more likely to use artificial sweeteners; 2) low or unequal response rates in case and control series would introduce a bias if respondents were systematically different from nonrespondents, as they often are; 3) history of smoking or occupational exposures and other potentially confounding variables were inadequately controlled; 4) slow identification of cases led to losses prior to interview; 5) the study of all hospitalized cases rather than just those newly diagnosed may lead to an unrepresentative sample of cases of bladder cancer; 6) the dose, timing, and type of exposure were not adequately ascertained; and 7) the numbers of cases and controls were too small to reveal a small increase in risk.

These studies do not provide enough evidence to establish an association between use of artificial sweeteners, specifically saccharin, and an increased risk of bladder cancer in humans. This review culminated in a report submitted to the Commissioner of the FDA by the Interagency Saccharin Working Group and contained a recommendation for the initiation of a new study.

PROPOSED NEW STUDY

The NCI will implement a large-scale population-based, case-control study with the use of cancer-reporting mechanisms of the NCI's SEER[4] program and the State Health Department of New Jersey. The SEER program is a collection of newly diagnosed cancer cases (except skin cancer) in about 10% of the U.S. population (slightly over 20 million people), which represents a wide geographic distribution. In addition to routinely collecting data on incidence, morbidity, and survival, it represents a valuable national resource for studies such as the one we propose. With the state of New Jersey, the SEER areas provide a unique, suitable, and existing resource for such a study. Collaborators' will share a common protocol, questionnaire, and operating procedures.

This combination of resources would provide: 1) data on 3,000–4,000 incident cases and 6,000–8,000 controls, which allow for the consideration of potential biasing factors, 2) a wide geographic base, 3) populations that experience a wide range of risks of bladder cancer, 4) a rapid report system for identifying newly diagnosed cases, 5) significant cost reductions through utilization of existing resources, 6) ongoing contracts that can be supplemented in a minimum amount of time, and 7) combined expertise of NCI–FDA epidemiologists, statisticians, and computer capabilities. We plan to begin collecting cases in February 1978 for 12 months. This procedure will allow 4 months for data analyses so that we hope to have some preliminary information by the end of the 18-month congressional action.

In summary, there is not enough evidence to establish an association between use of artificial sweeteners, specifically saccharin, and an increased risk of bladder cancer in humans. The NCI with the FDA is initiating a large-scale study of saccharin use and bladder cancer. This effort is a good example of collaboration by a research institute and a regulatory agency to work on a problem of public importance.

[4] The study includes four states and six metropolitan areas: Connecticut, Iowa, New Mexico, Utah, Detroit, San Francisco, Oakland, New Orleans, Atlanta, and Seattle.

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